

CD4 cells count as a prognostic marker in HIV patients with comparative analysis of various studies in Asia Pacific region

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ABSTRACT

Purpose: To evaluate the correlation between CD4+ cells count with orofacial and systemic manifestations in newly diagnosed HIV seropositive patients and comparison of results with the previous studies. **Materials and Methods:** Hundred (100; 57 males and 43 females) newly diagnosed HIV seropositive patients, before starting antiretroviral therapy (ART) were included in the study. These patients were clustered according to CD4+ cells count into three groups: 0–200 cells/mm³, 201–499 cells/mm³, and more than 500 cells/mm³. Orofacial and systemic manifestations of these patients were recorded and correlated with CD4 cells count values. **Results:** There was no significant correlation found between CD4+ cells count values of males and females using independent *t*-test. Chi-square test showed significant correlation between the systemic manifestations and CD4+ cells count categories. Tuberculosis was found to be the most common systemic manifestation in both the genders. In addition, a significant correlation was between the CD4+ cells count and orofacial manifestations, where oral candidiasis was found to be the most common manifestation in both the genders. **Conclusion:** The prevalence of systemic and orofacial manifestations increases with decrease in the CD4+ cells count of HIV seropositive patients. Hence, it can be used as diagnostic and prognostic marker for immune suppression in HIV positive patients.

Keywords: Antiretroviral therapy, candidiasis, orofacial manifestations, systemic manifestations, tuberculosis

Introduction

Acquired immunodeficiency syndrome (AIDS) is a disease caused by human immunodeficiency virus (HIV) infection which emerged as a pandemic in the last three decades.^[1] Approximately,

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37.9 million people are living globally with this infection and 24.5 million are on ART therapy (end of June 2019). India itself accounts for the third-largest number of HIV infected people in the world (around 2.1 million) after South Africa and Nigeria. However, UNAIDS (2018) data suggested a marked decrease in the number of new infections and AIDS related deaths by 27% and 56%, respectively, from the period of 2010-17. The same data also estimated HIV prevalence among adults in India (aged 15–49 years) to be 0.2%, in which, 79% of them were aware of their HIV status and 56% of them were on the antiretroviral

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therapy (ART). Therefore, HIV infection is still a major health concern in India.^[2] HIV is a retrovirus which affects the human immune system. This virus hinders the body's defense mechanism by depletion of cluster of differentiation 4 (CD4) cells.^[3] When newly produced CD4+ cells cannot replace the destroyed ones, it results in shutting down of the immune system leading to AIDS. As a result of the immunosuppression, people living with AIDS become susceptible to systemic opportunistic infections and malignancies. However, oral lesions are generally the primary sign of HIV/AIDS infections. These oral lesion plays an important in diagnosis as well as the prognosis of the disease because the severity of the oral lesions correlates with the decrease in the number of CD4+ cells count.^[4,5] Many studies have shown discrepancies among these oral manifestations according to development status and continents. It can be explained by the disparity in health care system, availability of ART, transmission route, gender, HIV stage, and deleterious habits. These specific oral and systemic manifestations are widely documented as well as correlated with CD4+ cells count in both developed and developing countries.^[6] But, in certain parts of the developing nations like India, the data is either negligible or none. Hence, we conducted this cross-sectional study among the newly diagnosed HIV seropositive patients in Gujarat (western India). The goal of the study was to evaluate the correlation between CD4+ cells count with orofacial and systemic manifestations.

Materials and Methods

Hundred (100; 57 males and 43 females) newly diagnosed HIV seropositive patients before starting ART were included into this cross-sectional study after the approval of institute research ethical committee SUVEC/ON/20/2007 (dated 20-08-2007) along with approval taken from NACO to conduct the study. Written informed consents were taken from all the participants in their regional language. The patients were selected from Outpatient Department of Infectious Disease (Dheeraj General Hospital, Vadodara), Department of Oral Medicine and Radiology (K. M. Shah Dental College and Hospital, Vadodara), and NGOs (Non-Governmental organizations) working for HIV positive individuals in Vadodara. Participants were excluded who were already started ART and who did not give informed consent. The personal and medical history along with the findings of Oral examination and Investigations were recorded in the performa specially designed for this study. Patients according to CD4+ cells count were clustered into three groups: Group A: 0–200 cells/mm³, Group B: 201–499 cells/mm³, and Group C: 500 cells/mm³. A single examiner trained in oral diagnosis examined and recorded all oral lesions. These

lesions were diagnosed according to presumptive criteria of EEC Clearinghouse Classification.^[7] Statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 21. Independent t-test was used to find a correlation between CD4 cells count of males and females. Chi-square test was used to find a correlation between the systemic manifestations and CD4+ cells count in different groups. It was also used to find a correlation between the oral manifestations and CD4+ cells count categories.

Results

The study group consisted of a total 100 HIV seropositive, 57 (57%) males and 43 (43%) females. The age range for study group was from 6 years to 65 years with mean age of 34.14 ± 11.51 years. In study group, out of total 57 males, 40 (70%) were married, 12 (21%) unmarried, 4 (7%) divorced, and 1 (1.75%) widow, whereas out of total 43 females, 25 (58.13%) were married, 5 (11.6%) unmarried, 2 (4.65%) divorced, and 11 (25.5%) were widows. The most common mode of HIV transmission was unprotected sexual practices (70%) followed by blood transfusion (18%), vertical transmission (9%), and intravenous drug users (3%). In study group, mean CD4 cells count in males was 253.51 ± 220.773 , whereas it was 230.86 ± 153.327 in females. On applying independent t-test, no correlation was found between CD4+ cells count of males and females (P -value > 0.005). In study group of 100 patients, 55% patients had CD4+ cells count below 200 (Group C), 34% had CD4 cells count between 201 and 499 (Group B), and 11% had CD4 cells count above 500 (Group A). Out of total 55 patients in group C, 34 (61.8%) and 54 (99%) patients had systemic and oral manifestations, respectively. In group B, out of 34 patients, 12 patients (35.2%) had systemic and 30 patients (88.2%) had oral manifestations. Only 2 (18.1%) patients out of 11 had systemic manifestations in group A with no oral manifestations as shown in Table 1. On applying Chi-square test, a significant correlation (P -value < 0.05) of CD4 cells count was found with the systemic and oral manifestations among three different groups. Out of total 57 males, 21 (36.8%) had tuberculosis followed by 3 (5.2%) cases of herpes zoster, 2 (3.5%) cases of pneumonia, and 1 (1.75%) case of typhoid, jaundice, and malaria each. Out of total 43 females, 13 (30.2%) cases had tuberculosis and 2 (4.6%) cases of pneumonia, anemia, and typhoid each. The most common systemic manifestation in both genders was tuberculosis [Table 2]. In the study group of 100 subjects, 17 (20.2%) cases had candidiasis, 14 (16.6%) cases chronic generalized periodontitis, 9 (10.7%) cases gingivitis, 7 (8.3%) cases aphthous, 6 (7.1%) cases premalignant lesions and conditions,

Table 1: Gender-wise distribution of systemic and oral manifestations among different groups based on CD4 cells count

Groups	CD4 cells count	Males	Females	Total	Systemic manifestations	Oral manifestations
A	>500	7	4	11	02	00
B	200-499	17	17	34	12	30
C	<200	33	22	55	34	54
Total		57	43	100	48	74

4 (4.7%) cases recurrent aphthous ulceration and angular cheilitis each, 3 (3.5%) cases erythema multiforme and hairy leukoplakia

Table 2. Gender-wise distribution of different systemic manifestations

Systemic manifestations	Male	Female	Total
Tuberculosis	21	13	34
Pneumonia	02	02	04
Anemia	00	02	02
Jaundice	01	00	01
Typhoid	01	02	03
Herpes	03	00	03
Malaria	01	00	01
Total	29	19	48

each, 2 (2.3%) cases herpes zoster, herpes labialis, and periodontal abscess each, and remaining others had single lesions like fissured tongue, mucous patches of secondary syphilis, acute necrotizing ulcerative periodontitis, linear gingival erythema, molluscum contagiosum, and oral pemphigus. A brief comparison of oral manifestations in HIV positive patients in our study and the previous studies conducted in Asia is shown in Table 3. The most common oral manifestation in males was found to be candidiasis 12 (21%) and chronic generalized periodontitis in 11 (19.2%) cases with an average CD4 cells count of 322.46 ± 219.14 and 191.76 ± 120.05 , respectively, whereas in females, the common oral manifestations were candidiasis and aphthous ulcers in 5 (11.6%) cases with an average CD4 cells count of 191.76 ± 120.05 and 130.08 ± 77.35 , respectively. The most frequently encountered

Table 3: A brief comparison of oral manifestations in HIV positive patients in our study and previous studies conducted in Asia

Country (Region)	Year	Study Sample size	OC %	CGP %	CGG/ LGE %	Aphthous %	PMLs %	AC %	OHL %	HZ %	HSV %	ANUP %	ANUG %	Oral melanosis %	Others %
India (west)	Present study	100	17	14	10	7	6	4	3	2	2	1	1	10	9
India (South)	2012	50	36	-	-	6	2	18	2	4	-	-	-	28	-
India	2012	604	32.2	-	-	4.4	-	-	-	3.3	-	-	-	-	-
India	2011	399	39.3	-	-	2.5	-	4.3	11.5	0.3	2	5.3	8.5	19.5	-
India (South)	2011	103	44	-	-	4.9	-	5.8	17.5	1.9	-	3.9	9.7	35.9	-
India	2011	124	32	-	-	-	-	-	4	-	-	-	-	31	-
India	2011	96	-	-	-	2.7	-	8.2	-	5.5	1.4	8.2	-	8.2	-
India	2010	321	11	17.3	-	4	-	0.6	2.8	-	3.1	-	-	1.2	-
India (South)	2009	200	-	-	-	5	-	9	18.5	1	2	7	9	33.5	-
India	2009	150	-	-	-	-	-	-	2.6	-	-	-	-	29.3	-
India (South)	2007	100	16	-	-	1	-	3	1	-	-	-	-	29	-
India (South)	2006	101	-	-	-	4.7	-	11.8	15.8	1.9	-	0.9	-	34.6	-
India	2004	1000	23.8	-	-	-	-	7.9	3.3	3.3	0.9	-	-	26.3	-
India	2004	410	36	-	-	3	-	1	3	-	5	-	-	3	-
India	2000	300	56	-	-	-	-	7.7	3	-	-	-	-	-	-
India	1997	96	81	-	-	6	-	-	-	-	-	-	-	-	-
Thailand	2010	207	-	82	-	3.2	-	-	2.5	-	-	-	-	38.2	-
Thailand	2004	237	40	14.5	-	5	-	3.5	29.5	-	-	0.5	1.5	-	--
Thailand	2001	87	-	-	-	-	-	6.9	11.5	-	1	-	-	-	-
Thailand	2001	364	39.6	-	-	-	-	18.3	26.3	-	-	-	-	-	-
Thailand	1997	41	76	-	-	-	-	-	7	-	-	-	-	-	-
Thailand	1997	214	66	-	-	-	-	-	13	-	-	-	-	-	-
Malaysia	1997	145	35.9	-	-	-	-	-	2.8	-	-	-	-	-	-
Hong Kong	1999	32	-	-	-	27.4	-	-	11	-	4.1	2.7	1.4	1.4	-
Japan	2000	110	15	-	-	-	-	-	1.8	-	-	-	-	-	-
Singapore	2001		35	16	-	-	-	-	5	-	-	-	-	-	-
Iran	2011	200	22	-	-	-	-	-	3	-	-	1.5	4	5.5	-
Iran	2010	100	-	44	-	-	-	17	4	-	-	-	-	42	-
Cambodia	2002	101	-	-	-	-	-	12.9	45.5	4	7.9	-	27.7	-	-
Georgia	2008	732	64	-	-	-	-	-	8	-	7	-	-	-	-
Taiwan	2004	64	71.1	-	-	-	-	-	8	-	-	-	-	-	-
Vietnam	2005	170	37.5	-	-	-	-	-	16.1	-	-	-	-	-	-

variant of candidiasis was pseudomembranous candidiasis in total 9 (52.9%) patients (5 males and 4 females), while 6 (35.2%) patients (5 males, 1 female) had erythematous candidiasis and only 2 (11.7%) patients (2 males) had hyperplastic type of candidiasis [Table 4].

Discussion

Numerous studies had been conducted to find the correlation of CD4+ cells count with the oral and systemic manifestations in HIV positive patients. Results of these studies had established CD4+ cells count as a diagnostic and prognostic marker for the immunosuppression in these patients.^[8-11] Oral cavity being the most dynamic part of the whole body get predispose to severe infections secondary to immunosuppression resulting in various HIV associated oral manifestations.^[12] These oral manifestations not only serve as an early sign of this infection but also clinically correlates with CD4+ cells count.^[13] Numerous studies have concluded that oral manifestations are of diagnostic and prognostic importance.^[10,11,13,14] These oral manifestations have shown discrepancies depending upon the regional/geographical variations and over different period of time.^[6,15] Hence, we conducted this cross-sectional study to evaluate the correlation between CD4+ cells count with orofacial and systemic manifestations among HIV seropositive patients in the third-largest Metropolis city of western Indian state of Gujarat. In the present study, there were 57 (57%) males and 43 (43%) females. This male predominance was in accordance with the findings of Ranganathan *et al.*^[16] but was in contrast to the findings of Annapurna *et al.*,^[10] where female predominance was present. In our study, there was no significant difference in the average CD4+ cells count of males and females, which was in contrast to the findings of the Ranganathan *et al.*^[8] Our study reported a significant correlation between the systemic manifestations and CD4+ cells count categories. There were 29 males and 19 females in which the systemic manifestations were recorded. Out of 29 males, 21 (72.4%) had tuberculosis followed by 3 (10.3%) cases of herpes zoster, 2 (6.8%) cases of pneumonia, and 1 (3.4%) case of typhoid, jaundice, and malaria each. Out of 19 females, 13 (68.4%) had tuberculosis and 2 (10.5%) cases of pneumonia, anemia, and typhoid each. The most common systemic manifestation in HIV positive males and females was tuberculosis (70.4%). This finding was congruent to the previous studies conducted by Ranganathan *et al.*^[8,16] Our study also reported a significant correlation between the oral manifestations and CD4+ cells count categories. The oral manifestations were seen in 30 (88.2%) and 54 (99%) individuals

in Groups B and C, respectively, whereas no oral manifestations were noted in Group A. A total of 84 (84%) patients had oral manifestations. The common oral manifestations recorded in males were, candidiasis (25%) followed by chronic generalized periodontitis (22.9%), aphthous stomatitis (16.6%), gingivitis (10.4%), and premalignant lesions (8.3%). The common oral manifestations recorded in females were candidiasis (13.8%) and aphthous stomatitis (13.8%) followed by chronic generalized periodontitis (8.3%), gingivitis (11.1%), and premalignant lesions (5.5%). A brief comparison of other oral manifestations in HIV positive patients in our study and the previous studies conducted in Asia^[15] is shown in Table 4. Unlike the previous studies, there was no significant difference was found in the prevalence of oral lesions in both sexes in our study.^[16,17-21] The most common oral manifestation in males and females was found to be candidiasis (19.4%) with the average CD4 cells count of 191 ± 120.05 and the most common variant of candidiasis encountered was pseudomembranous type. These results are consistent with findings of other investigators who examined oral lesions and conditions associated with HIV positive patients.^[8,14,18-26]

Conclusion

In our study, we concluded that the most common cause of HIV among males was unprotected sexual practices with multiple partners including commercial sex workers by heterosexual route and most of women had acquired HIV infection from their infected spouses. There was no significant difference in the average CD4+ cells count of males and females. The most common systemic manifestation of HIV positive patients in both males and females was tuberculosis. Oral manifestations were recorded in almost all HIV positive patients with CD4 cells count below 500. There was equal prevalence of oral manifestations in both genders. Most common oral manifestation in both males and females was candidiasis with CD4+ cells count below 200. Hence, we can conclude that oral manifestations/lesions are the hallmarks of this infection. It directly reflects the extent of systemic immunosuppression of the infected individual. Therefore, oral physician should be capable to diagnose these lesions and should provide guidance to the patient for the early diagnosis and treatment of this life-threatening infection.

Key message: Hence, we can conclude that the oral manifestations/lesions are the hallmark of HIV infection. It directly reflects the extent of systemic immunosuppression of the infected individual. Therefore, oral and general physician

Table 4: Most common oral manifestation in males and females of HIV positive patients

Oral Manifestations	Total (n=84)	Males (n=48)	Females (n=36)	Avg CD4 cells Count	Std Deviation
Candidiasis	17	12	5	191.76	120.05
Chronic Generalized Periodontitis	14	11	3	322.466	219.14
Aphthous	13	8	5	130.08	77.35
Melanosis	10	5	5	244.7	182.33
Gingivitis	9	5	4	553.4	273.96
Premalignant Lesions	6	4	2	221.857	99.8

should be capable to diagnose these lesions and should provide guidance to the patient for the early diagnosis and treatment of this life-threatening infection which will help the patient. Early diagnosis of the disease will help in primary care of diagnosed HIV cases and also if the physician has the slightest suspicion while screening the oral cavity, they can motivate the patient for HIV testing and further investigations.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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